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Synthesis of (+)-(1*S*,2*R*) and (–)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acids

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Abstract—(+)-(1*S*,2*R*) and (–)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acids have been prepared in >97% ee and in 33% and 20% overall yields starting from a single, chiral, bicyclic compound perceived as a chiral uracil equivalent. Construction of the cyclobutane ring is achieved via a [2+2] photocycloaddition reaction of this chiral precursor with ethylene.

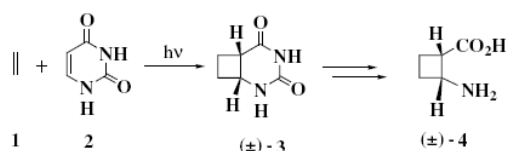
The incorporation of conformationally constrained β -amino acids into peptides can dramatically influence their secondary and tertiary structures and biological activities.¹ In consequence, interest for the synthesis and study of alicyclic β -amino acids has rapidly increased.² Most efforts are devoted to cyclohexane,³ cyclopentane⁴ and cyclopropane⁵ derivatives. Indeed, oligopeptide chains containing *trans*-2-aminocyclohexanecarboxylic acid have been shown to adopt 14-helical structures while those containing *trans*-2-aminocyclopentanecarboxylic acid prefer 12-helices.^{3b} *cis*-Cyclopropane derivatives, too, give highly stable helical conformations in peptides.^{5c} Moreover, some alicyclic β -amino acid derivatives display antifungal, antibiotic or analgesic activities.^{2,6} Despite the clear potential of cyclobutane β -amino acid building blocks in this context, and some positive indications of their ability to impose secondary structure from preliminary studies,^{7,8a} there are currently very few means of access to these compounds.

Only two enantioselective syntheses of *cis*-2-aminocyclobutane-1-carboxylic acid have been described so far: first by Martín-Vilà et al.⁸ and then recently by Bolm et al.⁹ Both procedures are based on an enantioselective *meso*-cyclobutane-1,2-dicarboxylic acid desymmetrization strategy, involving enzymatic hydrolysis of a diester in

the first case and alkaloid-mediated opening of the anhydride in the second. Subsequent transformations led to the (–)-(1*R*,2*S*) antipode in each case. We present here an alternative strategy allowing rapid access to both enantiomers using simple and easily accessible materials.

We previously described the synthesis of racemic 2-aminocyclobutane-1-carboxylic acid (\pm)-4.¹⁰ The strategy was based on a photochemical reaction of ethylene (1) with uracil (2) to give the cyclobutane adduct (\pm)-3, followed by controlled degradation of the heterocyclic ring. The target amino acid (\pm)-4 was obtained with an overall yield of 52% (Scheme 1).

Our aim was to develop an enantioselective version of this synthesis. To this end, we decided to introduce a chiral auxiliary on the uracil ring in order to induce diastereochemical discrimination of cyclobutane adducts. There was also the possibility for diastereofacial selection during the photochemical [2+2] reaction,¹¹ although results with ethylene as one of the reaction components are highly variable.¹² We selected to use



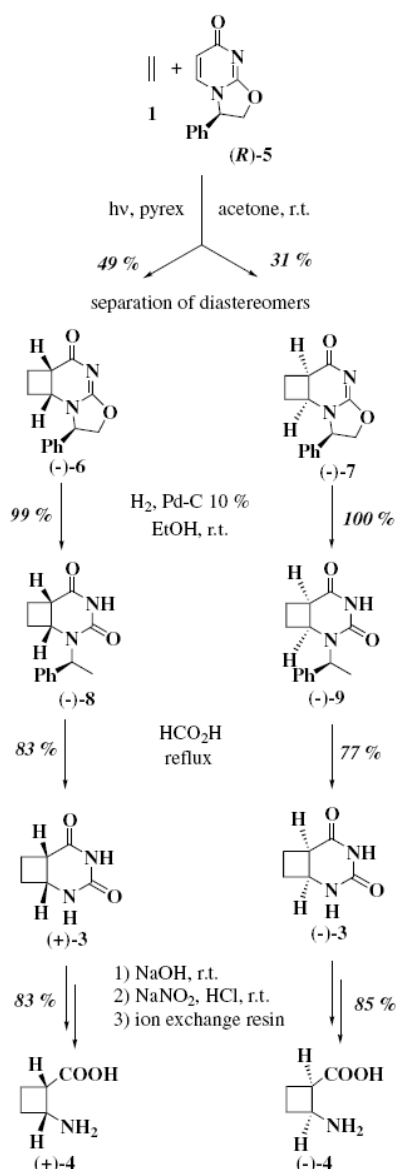
Scheme 1.

Keywords: β -Amino acid; Cyclobutane; Stereoselective synthesis; [2+2] Photocycloaddition reaction.

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the *N*1-substituted uracil mimic (*R*)-**5**. This bicyclic compound was easily obtained in enantiomerically pure form in two steps from commercial (*R*)-phenylglycinol, essentially as described by Agami et al. for the *S*-enantiomer.¹³

Compound (*R*)-**5** was submitted to [2+2] photocycloaddition reaction conditions (Scheme 2). Ethylene (**1**) was bubbled through a solution of (*R*)-**5** in acetone at room temperature, which was irradiated with a 400 W medium-pressure mercury lamp fitted with a Pyrex filter during 2 h. In the event, the desired cyclobutane adduct was obtained as a mixture of two diastereoisomers. In conformity with our previous study involving uracil **2** (Scheme 1),¹⁰ cyclobutane compounds (–)-**6** and (–)-**7** each had a *cis* configuration; a de of 14% was determined by integration of ¹H NMR data obtained on the crude material. Separation was easily achieved by



Scheme 2.

column chromatography on silica gel, giving both (–)-**6** and (–)-**7** in stereochemically pure form in 49% and 31% yield, respectively. Subsequent transformations were carried out under identical conditions for each pure compound.

Selective opening of the five-membered rings of (–)-**6** and (–)-**7** was achieved by catalytic hydrogenation in the presence of palladium on charcoal, as described by Agami et al. for related heterocyclic structures.¹³ Single diastereoisomers (–)-**8** and (–)-**9** were thus obtained in effectively quantitative yield.

Next, the α -methylbenzyl group was removed cleanly and efficiently with refluxing formic acid.¹⁴ We thus obtained enantiomers (+)-**3** and (–)-**3** whose spectroscopic data were identical with those of our previous sample of (\pm)-**3**.¹⁰ The two-step transformation of the heterocyclic ring—involving mild base hydrolysis followed by diazotization with 1 equiv of sodium nitrite in acidic medium—followed by purification on ion exchange resin proceeded in good yield without trace of epimerization and led to the target β -amino acids (+)-**4** and (–)-**4** in zwitterionic form (Scheme 2). NMR spectroscopic data¹⁵ were comparable with those for racemic material¹⁰ and with those reported by Bolm et al.⁹ for (–)-**4**.

The overall yields following this short sequence were 33% and 20% for (+)-**4** and (–)-**4**, respectively, from (*R*)-**5**. Their respective optical rotations were +71 (*c* 0.88, H₂O) and –70 (*c* 1.03, H₂O). We determined an enantiomeric excess of >97% for each enantiomer (+)-**4** and (–)-**4** by HPLC on chiral column.¹⁶ Since the ee of (*R*)-**5** was 98%, as determined by ¹H NMR with the chiral shift reagent Eu(hcf)₃, we can conclude that there was no loss of stereochemical fidelity during the synthesis.

The attribution of the 1*R*,2*S* absolute configuration of the β -amino acid (–)-**4** was made by correlation with the previous observations made by Martín-Vilà et al.⁸ and Bolm et al.⁹ The absolute configuration of (+)-**4** is therefore 1*S*,2*R*.

In summary, we have succeeded in synthesizing both (+)-(1*S*,2*R*) and (–)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acid **4** in five steps from (*R*)-**5**. Previous desymmetrization based stereoselective syntheses started with derivatives of *cis*-cyclobutane-1,2-dicarboxylic acid, which, although commercially available, is rather expensive. Our synthesis represents a useful complementary strategy and provides the first described access to the (+) antipode.¹⁷ Millimolar-range quantities of the title β -amino acids are routinely accessible in this way and their incorporation into peptides is currently under study.

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mont-Ferrand) and P. Ferchaud (Poitiers) for carrying out some initial experiments competently.

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15. Compounds (+)-4 and (–)-4: ¹H NMR (400 MHz, D₂O, calibration on 1,4-dioxane at δ_{H} 3.75 ppm) δ 1.75 (m, 1H), 1.95 (m, 2H), 2.03 (m, 1H), 2.92 (m, 1H), 3.61 (q, 1H, J = 6.8 Hz); ¹³C NMR (100 MHz, D₂O, calibration on 1,4-dioxane at δ_{C} 67.2 ppm) δ 21.2, 25.0, 41.3, 45.5, 181.0.
16. HPLC analysis was performed using a Waters 590 apparatus equipped with a Waters 484 UV detector and a Crownpak CR(+) column (0.4 × 15 cm) with the following conditions: perchloric acid solution (pH = 1) as mobile phase; T = 4°C; λ = 220 nm; flow rate = 0.2 mL/min. Retention times: (+)-4: 12.20 min; (–)-4: 19.48 min.
17. It is also worth noting that this route incurs no difficulties related to the facile ring-opening propensity of the final products; see: Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2004**, *45*, 2359–2361.